Chapter 1

Principles of Vaccination

Milestones in the History of Vaccination

1100s Variolation for smallpox first reported in China
1721 Variolation introduced into Great Britain
1796 Edward Jenner inoculates James Phipps with cowpox, and calls the procedure vaccination ("vacca" is Latin for cow).
1870 Louis Pasteur creates the first live attenuated bacterial vaccine (chicken cholera)
1884 Pasteur creates the first live attenuated viral vaccine (rabies)
1885 Pasteur first uses rabies vaccine in a human
1901 First Nobel Prize in Medicine to von Behring for diphtheria antitoxin
1909 Smith discovers a method for inactivating diphtheria toxin
1909 Calmet and Guerin create BCG, the first live attenuated bacterial vaccine for humans
1933 Goodpasture describes a technique for viral culture in hen's eggs
1949 Enders and colleagues isolate Lansing Type II poliovirus in human cell line
1954 Enders isolates measles virus
1955 Inactivated polio vaccine licensed
1961 Human diploid cell line developed
1963 Measles vaccine licensed
Trivalent oral polio vaccine licensed
1966 World Health Assembly calls for global smallpox eradication
1977 Last indigenous case of smallpox (Somalia)
1979 Last wild-virus polio transmission in the U.S.
1986 First recombinant vaccine licensed (hepatitis B)
1989 Two-dose measles vaccine recommendation
1990 First polysaccharide conjugate vaccine licensed (*Haemophilus influenzae* type b)
1991 Last wild-virus polio case in the Western Hemisphere
Universal infant hepatitis B vaccination recommended
1994 Polio elimination certified in the Americas
1995 Varicella vaccine licensed
1996 Acellular pertussis vaccine licensed for infants
1997 Sequential polio vaccination recommended
1999 Exclusive use of inactivated polio vaccine recommended
2000 Conjugate pneumococcal vaccine licensed for infants

Immunology and Vaccine-Preventable Disease

Immunology is a complicated subject, and a detailed discussion of it is beyond the scope of this text. However, an understanding of the basic function of the immune system is useful in order to understand both how vaccines work and the basis of recommendations for their use. The description that follows is simplified. Many excellent immunology textbooks are available to provide additional detail.

Principles of Vaccination

Immunity
- **Self vs. non-self**
- **Protection from infectious disease**

Protection from infectious disease is referred to as **immunity**. There are two basic mechanisms for acquiring this protection — active and passive.

Active immunity is protection that is produced by the person's own immune system. This type of immunity is usually permanent.

Passive immunity is protection by products produced by an animal or human, and transferred to another human, usually by injection. Passive immunity often provides effective protection, but this protection wanes (disappears) over time, usually a few weeks or months.

Principles of Vaccination
- **Immunity**
  - **Self vs. non-self**
  - **Protection from infectious disease**
- **Active Immunity**
  - **Protection produced by a person's own immune system**
  - **Usually permanent**
- **Passive Immunity**
  - **Protection transferred from another person or animal as antibody**

The **immune system** is a complex system of interacting cells whose primary purpose is to identify foreign ("non-self") substances referred to as **antigens**. Antigens can be either live (such as viruses and bacteria) or inactivated. The immune system develops a defense against the antigen. This defense is known as the **immune response** and usually involves the production of protein molecules, called **antibodies** (or immunoglobulins), and of specific cells (also known as **cell-mediated immunity**) whose purpose is to facilitate the elimination of foreign substances.

The most effective immune responses are generally produced in response to a live antigen. However, an antigen does not necessarily have to be alive, as in a natural infection with a virus or bacteria, to produce an immune response. Some proteins, such as hepatitis B surface antigen, are easily recognized by the immune system. Other material, such as polysaccharide (long chains of sugar molecules that make up the cell wall of certain bacteria) are less effective antigens, and the immune response may not provide as good protection.

Principles of Vaccination

Antigen
- **A live or inactivated substance (e.g., protein, polysaccharide) capable of producing an immune response**

Antibody
- **Protein molecules (immunoglobulin) produced by B lymphocytes to help eliminate an antigen**

An immune response is generally specific to the organism or antigen that produced it. For example, antibodies produced in response to measles virus have no effect on rubella or influenza viruses.

Passive immunity

Passive immunity is the transfer of antibody produced by one human or animal to another. Passive immunity provides protection against some infections, but this protection is temporary. The antibodies will degrade over a period of weeks to months and the recipient will no longer be immune.

Passive Immunity

- **Antibody transferred from another person or animal**
- **Transplacental most important source in infancy**
- **Temporary protection**

The most common form of passive immunity is that which an infant receives from its mother. Antibodies are transported across the placenta during the last 1-2 months of pregnancy. As a result, a full-term infant will have the same antibody "profile" as its mother. These antibodies will protect the infant from certain diseases for up to a year. Protection is better against some diseases (*e.g.*, measles, rubella, tetanus) than others (*e.g.*, polio, pertussis).

Virtually all types of blood products contain antibody. Some products (*e.g.*, washed or reconstituted red blood cells) contain a relatively small amount of antibody, and some (*e.g.*, intravenous immune globulin and plasma products) contain very large amounts.

Besides blood products used for transfusion (*e.g.*, whole blood, red cells, and platelets) there are three major sources of antibody used in human medicine. These are (1) homologous pooled human antibody (immune globulin), (2) homologous human hyperimmune globulin, and (3) heterologous hyperimmune serum (antitoxin).

Homologous pooled human antibody is also known as **immune globulin**. It is produced by combining (pooling) the IgG antibody fraction from thousands of adult donors in the U.S. Because it comes from many different donors, it contains antibody to many different antigens. It is used primarily for post-exposure prophylaxis for hepatitis A and measles.

Types of Passive Immunity

- **Homologous pooled human antibody (immune globulin)**
- **Homologous human hyperimmune globulin**
- **Heterologous hyperimmune serum (antitoxin)**

Homologous human hyperimmune globulins are antibody products that contain high titers of specific antibody. These products are made from the donated plasma of humans with high levels of the antibody of interest. However, since hyperimmune globulins are from humans, they also contain other antibodies in smaller quantities.

Hyperimmune globulins are used for post-exposure prophylaxis for several diseases, including hepatitis B, rabies, tetanus, and varicella.

Two globulin products are available for the treatment of respiratory synctial virus (RSV) infection- RSV-IGIV and Palivizumab (Synagis). RSV-IGIV is a hyperimmune globulin from human donors. It contains antibody other than RSV, like other hyperimmune globulin products. Palivizumab is a humanized monoclonal antibody specific for RSV. It does not contain any other antibody except anti-RSV antibody.

Heterologous hyperimmune serum is also known as **antitoxin**. This product is produced in animals, usually horses (equine), and contains antibodies against only one antigen. In the U.S., antitoxin is available for treatment of botulism and diphtheria. A problem with this product is serum sickness, a reaction to the horse protein.

Active immunity

Active immunity is stimulation of the immune system to produce antigen-specific humoral (antibody) and cellular immunity. Unlike passive immunity which is temporary, active immunity usually lasts for many years, often for a lifetime.

One way to acquire active immunity is to have the natural disease. In general, once persons recover from infectious diseases, they will be immune to those diseases for the rest of their lives. The persistence of protection for many years after the infection is known as **immunologic memory**. Following exposure of the immune system to an antigen, certain cells (memory B-cells) continue to circulate in the blood (and also reside in the bone marrow) for many years. Upon reexposure to the antigen, these memory cells begin to replicate and produce antibody very rapidly to reestablish protection.

Vaccination

- **Active immunity produced by vaccine**
- **Immunity and immunologic memory similar to natural infection but without risk of disease**

Another way to produce active immunity is by **vaccination**. Vaccines interact with the immune system and often produce an immune response similar to that produced by the natural infection, but do not subject the recipient to the disease and its potential complications. Vaccines produce immunologic memory similar to that acquired by having the natural disease.

Many factors may influence the immune response to vaccination. These include the presence of maternal antibody, nature and dose of antigen, route of administration, and the presence of adjuvants (*e.g.*, aluminum-containing materials added to improve the

immunogenicity of the vaccine). Host factors such as age, nutritional factors, genetics, and coexisting disease, may also affect the response.

Classification of Vaccines

There are only two basic types of vaccines: **live attenuated** and **inactivated**. The characteristics of live and inactivated vaccines are different, and these characteristics determine how the vaccine is used.

Live attenuated vaccines are produced by modifying a disease-producing ("wild") virus or bacteria in a laboratory. The resulting vaccine organism retains the ability to replicate (grow) and produce immunity, but usually does not cause illness. Live attenuated vaccines available in the U.S. include live viruses and live bacteria.

Inactivated vaccines can be composed of either **whole** viruses or bacteria, or fractions of either. **Fractional** vaccines are either protein-based or polysaccharide-based. Protein-based vaccines include **toxoids** (inactivated bacterial toxin), and **subunit** or subvirion products. Most polysaccharide-based vaccines are composed of pure cell-wall polysaccharide from bacteria. **Conjugate** polysaccharide vaccines are those in which the polysaccharide is chemically linked to a protein. This linkage makes the polysaccharide a more potent vaccine.

General Rule

The more similar a vaccine is to the natural disease, the better the immune response to the vaccine.

Live attenuated vaccines

Live vaccines are derived from "wild," or disease-causing, virus or bacteria. These wild viruses or bacteria are attenuated, or weakened, in a laboratory, usually by repeated culturing. For example, the measles vaccine used today was isolated from a child with measles disease in 1954. Almost 10 years of serial passage on tissue culture media was required to transform the wild virus into vaccine virus.

In order to produce an immune response, live attenuated vaccines must replicate (grow) in the vaccinated person. A relatively small dose of virus or bacteria is given, which replicates in the body and increases to a volume large enough to stimulate an

Classification of Vaccines

- **Live attenuated**
- **Inactivated**

Live Attenuated Vaccines

- **Viral**
- **Bacterial**

Inactivated Vaccines

Whole
- **virus**
- **bacteria**

Fractional
- **protein-based**
  - **subunit**
  - **toxoid**
- **polysaccharide-based**
  - **pure**
  - **conjugate**

Live Attenuated Vaccines

- **Attenuated (weakened) form of the "wild" virus or bacteria**
- **Must replicate to be effective**
- **Immune response similar to natural infection**
- **Usually effective with one dose**

immune response. Anything that either damages the live organism in the vial (*e.g.*, heat, light), or interferes with replication of the organism in the body (circulating antibody) can cause the vaccine to be ineffective.

Although live attenuated vaccines replicate, they usually do not cause disease, such as may occur with the natural ("wild") organism. When a live attenuated vaccine does cause "disease," it is usually much milder than the natural disease, and is referred to as an adverse reaction.

Live Attenuated Vaccines

- **Severe reactions possible**
- **Interference from circulating antibody**
- **Unstable**

The immune response to a live attenuated vaccine is virtually identical to that produced by a natural infection. The immune system does not differentiate between an infection with a weakened vaccine virus and an infection with a wild virus. Live attenuated vaccines are generally effective with one dose, except those administered orally.

Live attenuated vaccines may cause severe or fatal reactions as a result of uncontrolled replication (growth) of the vaccine virus. This only occurs in persons with immunodeficiency (*e.g.*, from leukemia, treatment with certain drugs, or HIV infection).

Live Attenuated Vaccines

- **Viral** — **measles, mumps, rubella, oral polio, vaccinia, varicella, yellow fever**
- **Bacterial** — **BCG, oral typhoid**

A live attenuated vaccine virus could theoretically revert back to its original pathogenic (disease-causing) form. This is known to happen only with live polio vaccine.

Active immunity from a live attenuated vaccine may not develop due to interference from circulating antibody to the vaccine virus. **Antibody from any source (*e.g.*, transplacental, transfusion) can interfere with growth of the vaccine organism and lead to nonresponse to the vaccine** (also known as vaccine failure). Measles vaccine virus seems to be most sensitive to circulating antibody. Polio and rotavirus vaccine viruses are least affected.

Live attenuated vaccines are labile, and can be damaged or destroyed by heat and light. They must be handled and stored carefully.

Currently available live attenuated vaccines include live viruses (measles, mumps, rubella, polio, yellow fever, vaccinia, and varicella), and two live bacterial vaccines (BCG and oral typhoid).

Inactivated Vaccines

- **Cannot replicate**
- **Generally not as effective as live vaccines**
- **Minimal interference from circulating antibody**

Inactivated vaccines

These vaccines are produced by growing the bacteria or virus in culture media, then inactivating it with heat and/or chemicals (usually formalin). In the case of fractional vaccines, the organism is further treated to purify only those components to be included in the vaccine (*e.g.*, the polysaccharide capsule of pneumococcus).

Inactivated vaccines are not alive and cannot replicate. The entire dose of antigen is administered in the injection. These vaccines cannot cause disease from infection, even in an immunodeficient person.

Unlike live antigens, inactivated antigens are usually not affected by circulating antibody. Inactivated vaccines may be given when antibody is present in the blood (*e.g.*, in infancy, or following receipt of antibody-containing blood products).

Inactivated vaccines always require multiple doses. In general, the first dose does not produce protective immunity, but only "primes" the immune system. A protective immune response develops after the second or third dose.

In contrast to live vaccines, in which the immune response closely resembles natural infection, the immune response to an inactivated vaccine is mostly humoral. Little or no cellular immunity results.

Antibody titers against inactivated antigens fall over time. As a result, some inactivated vaccines may require periodic supplemental doses to increase, or "boost," antibody titers.

In some cases, the antigen critical to protection against the disease may not be defined, thus requiring the use of "whole cell" vaccines. Whole cell bacterial vaccines are typically the most reactogenic (*i.e.*, cause the most adverse events). This is because of responses to cell components that may not be needed for protection.

Currently available inactivated vaccines include inactivated whole viruses (influenza, polio, rabies, hepatitis A) and inactivated whole bacteria (pertussis, typhoid, cholera, plague). "Fractional" vaccines include subunits (hepatitis B, influenza, acellular pertussis, typhoid Vi, Lyme disease), toxoids (diphtheria, tetanus, botulinum), pure polysaccharides (pneumococcal, meningococcal, *Haemophilus influenzae* type b), and polysaccharide conjugates (*Haemophilus influenzae* type b and pneumococcal).

Polysaccharide vaccines

Polysaccharide vaccines are a unique type of inactivated subunit vaccine composed of long chains of sugar molecules that make up the surface capsule of certain bacteria. Pure polysaccharide vaccines are available for three diseases: pneumococcal disease, meningococcal disease, and *Haemophilus influenzae* type b.

Inactivated Vaccines

- **Generally require 3-5 doses**
- **Immune response mostly humoral**
- **Antibody titer falls over time**
- **Principal antigen may not be defined**

Inactivated Vaccines

Whole cell vaccines

- **Viral** — **influenza, polio, rabies, hepatitis A**
- **Bacterial** — **pertussis, typhoid, cholera, plague**

Inactivated Vaccines

Fractional vaccines

- **Subunit** — **hepatitis B, influenza, acellular pertussis, typhoid Vi, Lyme disease**
- **Toxoid** — **diphtheria, tetanus**

Polysaccharide Vaccines

Pure polysaccharide

- **pneumococcal**
- **meningococcal**
- ***Haemophilus influenzae* type b**

Conjugate polysaccharide

- ***Haemophilus influenzae* type b**
- **pneumococcal**

Pure Polysaccharide Vaccines

- **Not consistently immunogenic in children <2 years of age**
- **No booster response**
- **Antibody with less functional activity**
- **Immunogenicity improved by conjugation**

The immune response to a pure polysaccharide vaccine is typically T-cell independent, which means that these vaccines are able to stimulate B-cells without the assistance of T-helper cells.

T-cell independent antigens, including polysaccharide vaccines, are not consistently immunogenic in children <2 years of age. Young children do not respond to polysaccharide antigens for reasons that are not clear. It probably has to do with immaturity of the immune system.

Repeat doses of polysaccharide vaccines do not cause a booster response. Repeated doses of most inactivated protein vaccines cause the antibody titer to go progressively higher, or "boost." This is not seen with polysaccharide antigens.

Antibody induced with polysaccharide vaccines has less functional activity than that induced by protein antigens. This is because the predominant antibody produced in response to polysaccharide vaccines is IgM, and little IgG is produced.

In the late 1980s, it was discovered that the problems noted above could be overcome through a process called conjugation. **Conjugation** changes the immune response from T-cell independent to T-cell dependent, leading to increased immunogenicity in infants and antibody booster response to multiple doses of vaccine.

The first conjugated polysaccharide vaccine was for *Haemophilus influenzae* type b (Hib). A conjugate vaccine for pneumococcal disease was recently licensed.

Recombinant vaccines

Vaccine antigens may also be produced by genetic engineering technology. These products are sometimes referred to as **recombinant** vaccines. Two genetically-engineered vaccines are currently available in the United States. Hepatitis B vaccines are produced by insertion of a segment of the hepatitis B virus gene into the gene of a yeast cell. The modified yeast cell produces pure hepatitis B surface antigen when it grows. Live typhoid vaccine (Ty21a) is *Salmonella typhi* bacteria that has been genetically modified to not cause illness.